

THE INFLUENCE OF EXTERNAL BODY RADIATION ON MORTALITY FROM THERMAL BURNS*

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THERMAL INJURY constituted a major medical problem following the atomic bomb attacks on Hiroshima and Nagasaki. From published reports and personal observation and discussions with Japanese medical scientists, it is apparent that after those attacks the bomb victims suffered from severe infection and malnutrition as well as burns.^{5, 9} Nevertheless, the mortality there from burns was so high as to make it difficult to explain on the basis of the thermal injury alone.

An analysis of the burn problem associated with atomic bomb attacks indicates that in the zone closest to the hypocenter, the bomb victim sustains injury from blast, burns and external body radiation, (gamma and neutrons). Attenuation of neutron and gamma radiation with increasing distances from the bomb burst is essentially different from that of thermal radiation (Fig. 1). Outside the 7000 ft. zone the victim receives little or no radiation from gamma rays or neutrons, but thermal energy dissipated as

ordinary heat is still powerful enough, even out to the 13,000 ft. zone, to produce burns on exposed body surfaces.

Of particular interest to our group is that intermediate zone, 4200 to 7000 ft. from the hypocenter, the "zone of combined radiation and thermal injury," where damage results from both gamma radiation and heat. Because external gamma radiation of 400 roentgens is probably in itself lethal, we have confined our interest to those levels of external body radiation (25 to 100r) which, by itself, is not lethal.

This study, therefore, has focused on what happens in the experimental animal (dog) when one inflicts at the same time moderate thermal injury *and* minor external body radiation injury, at levels so minor that each, when inflicted alone, is relatively non-lethal; all of this in an effort to understand better the fundamental mechanisms responsible for the high mortality of bomb victims who may be caught in the outer portions of that zone of combined thermal and radiation injury at the time of the bomb burst.

CONDUCT OF EXPERIMENT

This study divides itself naturally into these categories: The effects of, (A) a standard 20 per cent contact burn alone, (B) 100r external body radiation alone, (C) the 20 per cent burn plus 25r external

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body radiation, (D) the 20 per cent burn plus 100r external body radiation, and (E) penicillin therapy in animals receiving the combined thermal and radiation injury.

Healthy, young adult dogs, male and female, were used in all experiments. They were selected and observed carefully for not less than two weeks and usually three weeks before being used. Every precaution was taken to ensure the use of only healthy animals. Details of animal selection and care are to be found in a previously published article.² The same precautions outlined there were followed strictly in this study.

A. A Standard 20 Per Cent Contact Burn Alone. A standard low temperature, contact burn was produced and its effect studied in 40 dogs. This burn is produced by contact with a heated brass plate, kept at a constant temperature of 60°C by circulating thermostatically controlled water, and held in contact with selected portions of the shaved skin for one minute. This plate is applied the requisite number of times to accomplish a 20 per cent area burn. The burn produced is similar to a deep second degree burn in human beings. In the first control series, no therapy was given after the burn was produced.³

B. 100r External Body Radiation Alone. Ten dogs, five males and five females, were given total body radiation of 100r alone. The roentgen ray apparatus used for whole body radiations was a 1000 KVP, resonant transformer, roentgen ray tube employing a tungsten target at right angles to the electron beam. Radiation emitted by the target at angles of 90° or more passed through a beryllium window side port, 2.5 cm. in diameter and 2 mm. thick. The anode extension was encased in a lead cylinder, one inch thick, having an aperture for the reflected beam; surrounding this cylinder was another lead cylinder, two inches thick, and containing a shutter mechanism operated by a solenoid. The shutter inter-

posed two inches of lead in the beam from the beryllium window; when open this shutter allowed the full width of the reflected beam to be brought out into the room.⁷

The dogs in this series were exposed at a focal skin distance of 200 cm. where the radiation field was within 10 per cent of its maximum value over the entire surface of the animal. The dosage rate through 1 mm. of aluminum filter was 17r/min. at 200 cm. as measured with Victoreen thimble chambers. The half-value-layer in lead was 0.75 mm. corresponding to an effective energy of about 0.2 Mev. Depth dosage measurements within a Masonite phantom indicated a half-value-layer in Masonite of approximately 15.0 cm.

Half of the total dosage, as measured in air, was delivered to each side of the dog. This necessitated turning off the roentgen ray machine long enough to reverse the dog's position. At a dosage rate of 17r/min, it required about 1.5 min. to deliver 25r, and about 6.5 min. to deliver 100r to each animal.

In these experiments neither the dosage rate nor the quality of radiation from our million volt roentgen ray apparatus corresponds to gamma ray exposures from an atomic bomb. This would require effective energies of 1 Mev or more, delivered at a dosage rate such that the animals would receive one half of the total dose in one second.⁴ Furthermore, during atomic explosions, both gamma ray exposure and thermal injury are inflicted simultaneously. To test the possible differences of the biologic effects of gamma radiation given before or after burning injury, we have irradiated some animals first and then inflicted thermal burns. The usual procedure, however, was to produce the thermal lesion first and then expose them to the roentgen ray beam. Within the limits of our clinical observation, the order of procedure has not produced detectable differences.

Dosage rates of this order of magnitude are not readily available. However, to the best of our knowledge, there is no reason to expect major biologic differences between whole body irradiations with 0.2 Mev roentgen rays and whole body exposures to gamma rays of 1 Mev or more. It is more difficult to assess the probable effects of the difference in dosage rates between our ex-

radiation immediately after. In others, the procedure was reversed.

E. *Penicillin Therapy in Animals Receiving the Combined Thermal and Radiation Injury.* Twenty-eight dogs, 18 males and ten females, were subjected to combined injuries as described under (D) above. Beginning 24 hours following injury they received 900,000 units of penicillin as pro-

TABLE I.—Analysis of The Physiologic Effects of Thermal Injury, External Body Radiation, and Their Combined Effects on the Dog.

Type of Experiment	Number of Animals	Mortality	Wound Healing Time (Weeks)	W.B.C. Thousands/cu.mm. 10th Day	Bone Marrow 7th Day	Blood Cultures 4-17 Days	Wound Cultures
20 per cent burn alone	40	12 per cent	6	36,000	Myeloid hyperplasia	Gamma streptococci 75 per cent	Beta and gamma streptococci
100R alone	10	0	0	8,300	No change
20 per cent burn plus 100R untreated	40	73 per cent	6	6,000	Diminished myeloid & erythroid elements	Gamma streptococci 78 per cent Beta streptococci 75 per cent	Beta and gamma streptococci
20 per cent burn plus 100R treated (penicillin)	28	14 per cent	5	15,400	Diminished myeloid & erythroid elements	Negative

periments and the bomb. In general, biologic damage would be expected to be more severe for the higher dosage rate.

C. *The 20 Per Cent Burn Plus 25r External Body Radiation.* Twenty-five dogs, ten males and 15 females, were given first a 20 per cent contact burn, followed immediately by 25r external body radiation. In this group the radiation injury was always preceded by the burn.

D. *The 20 Per Cent Burn Plus 100r External Body Radiation.* Forty dogs, 15 males and 25 females, were given a deep second degree burn by the low temperature contact method which involved 20 per cent of the body skin surface area. Each of these animals then received 100r of total body gamma irradiation. In some the thermal injury was inflicted first, the external body

caine-penicillin aqueous suspension daily in one intra-muscular injection for 17 days.

FEATURES STUDIED IN EACH EXPERIMENT

Blood was drawn from the jugular veins, a total of 3.0 cc. daily five days a week for 21 days. Thereafter, blood was drawn three days weekly until the termination of the experiment. Heparin was used as the anti-coagulant. Body weight and rectal temperature of each animal were recorded at the time each sample was drawn.

The following hematology studies were done on each blood sample drawn:

a. *Hemoglobin.* Duplicate determinations of oxyhemoglobin using the Junior Coleman spectrophotometer.¹

b. *Hematocrit.* With Wintrobe hematocrit tubes.¹¹

c. *Red Blood Cell Count.* Single determinations.¹²

d. *White Blood Cell Count.* Duplicate counts for each sample with the average recorded as this value.¹²

e. *Differential Count.* Wright's stain for staining and 100 cells counted for each determination.¹²

h. *Bone Marrow.* Wright's stain was used for staining and 1000 cells were counted on each slide. Two slides were counted for each determination. Bone marrow studies made weekly; for, marrow was obtained from iliac crests.

i. *Blood Cultures.* Bacto-tryptose, dextrose agar and broth media were used. The

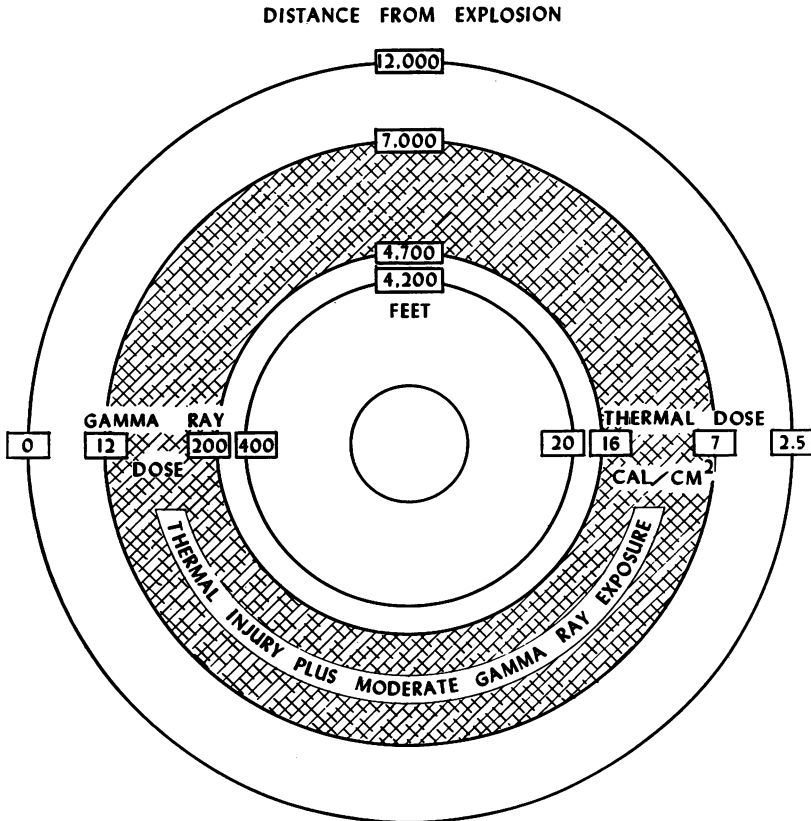


FIG. 1.—Thermal and gamma ray exposures at various distances from nominal bomb, assuming negligible atmospheric attenuation.

f. *Total Plasma Proteins.* By copper sulfate specific gravity method.¹⁰

g. *Plasma Volume.* Using T₁₈₂₄ Evans blue dye.⁸ One blood sample was drawn 12 min. after the dye injection. An additional 10.0 cc. of blood was drawn on the days that blood volumes were studied. These determinations were made on several occasions during the control period and once each week following injury.

culture flasks were prepared essentially according to the methods described by Castaneda,³ the only modification being the addition of 0.1 per cent yeast extract to the medium. Blood specimens taken from the dogs in 5 ml. amounts were inoculated directly into the bottles of culture media. All cultures were incubated aerobically at 37°C and examined each day for evidence of growth. If no growth appeared in the cul-

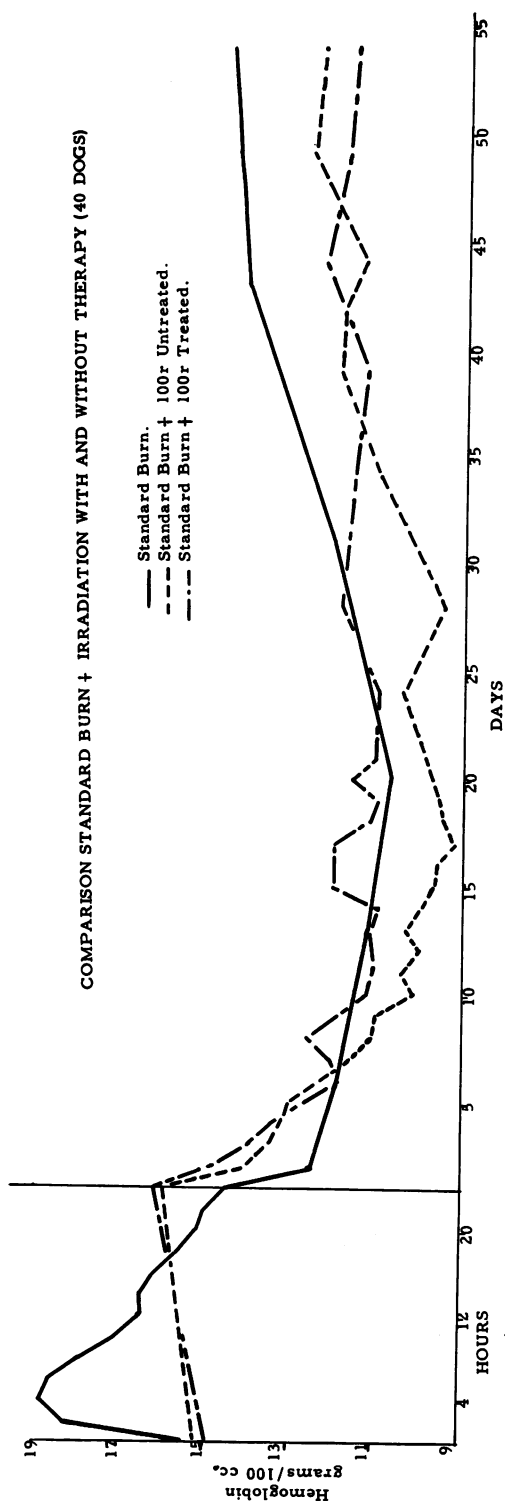


FIG. 2.—In the 0 to 24-hour period, hemococoncentration of the same magnitude occurred in the irradiated dogs as in those burned alone. This has not been indicated in either Figure 2 or 3.

ture flask at the end of five days incubation, the culture was discarded as negative. Positive cultures were identified by appropriate procedures described below. Initially, duplicate cultures were run on each blood specimen, one of which was incubated under aerobic conditions and the other under anaerobic conditions. When it was found that the septicemia occurring in the animals was in all cases due to aerobic bacteria, the anaerobic cultures were discontinued.

j. *Wound Cultures and Identification of Bacteria.* Cultures of the wounds were made with sterile cotton swabs which were then streaked directly on blood agar plates. These plates were examined after 24 and 48 hours incubation at 37°C. The predominating organisms present in the wounds were streptococci and staphylococci. Representative colonies were picked from the plates to blood agar slants for further identification.

Bacteria isolated from the blood and wounds of the animals were identified by the following procedures: Preliminary grouping of the streptococci was made into alpha hemolytic, beta hemolytic and gamma types as determined by their reaction on blood agar plates. The beta hemolytic streptococci were further subdivided serologically by means of their group-carbohydrate C substance according to the method described by Lancefield. Because of the unsatisfactory criteria for distinguishing many of the species within the alpha hemolytic and gamma types they were not further differentiated.

All staphylococci isolated were identified as either *Staphylococcus aureus* or *Staphylococcus albus* on the basis of pigment formation. The hemolytic and coagulase activity also was determined for each strain. Staphylococci were found only occasionally in these burn wounds and appeared to play little, if any, role in the septicemia of the experimental animals.

k. *Wound Healing Time.* Clinical and microscopic evidence was obtained.

RESULTS OF OBSERVATIONS

The 20 Per Cent Standard Burn Alone. During the early hours following burning, the course of the hemoconcentration was similar to that noted in humans with burns of comparable extent (Figs. 2 and 3). The plasma loss by measurement was approximately 1.0 cc. per kilogram of body weight per per cent body surface area burned; these data form the basis for the formula we are using for the clinical management of shock therapy in the severely burned patient.⁶

Anemia was noted early in the post-burn period and progressed from an average control value of 14.9 Gm. to an average low point of 10.7 Gm. on the twentieth day post burn. Recovery was gradual but complete by the sixtieth day following injury (Figs. 2 and 3).

Local wound infection was at a maximum on the tenth day, corresponding to the peak of the leukocyte response. The W.B.C. rose from an average control level of 14,500 W.B.C./cu.mm. to 36,000 W.B.C./cu.mm. on the tenth day. There was noted a marked shift to the left, many bend forms, toxic granules, and bone marrow evidence of greatly increased myeloid activity (Fig. 4). This infection was apparently rapidly brought under control without antibiotic therapy and the leukocyte count rapidly returned to approximately control levels by the third week. The average healing time for these burn wounds was six weeks.

Wound culture studies showed a variety of organisms, the most consistent being alpha, beta and gamma streptococci. Blood culture studies were positive for gamma streptococci in 78 per cent of animals in this group on varying days between the fifth and seventeenth days following injury.

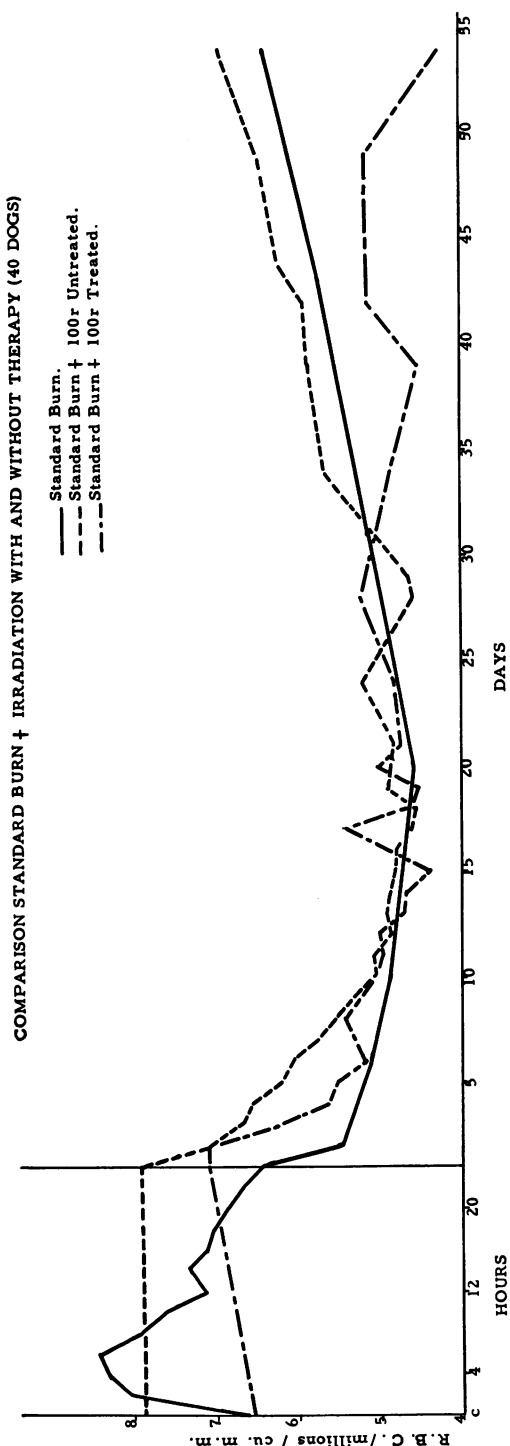


FIG. 3

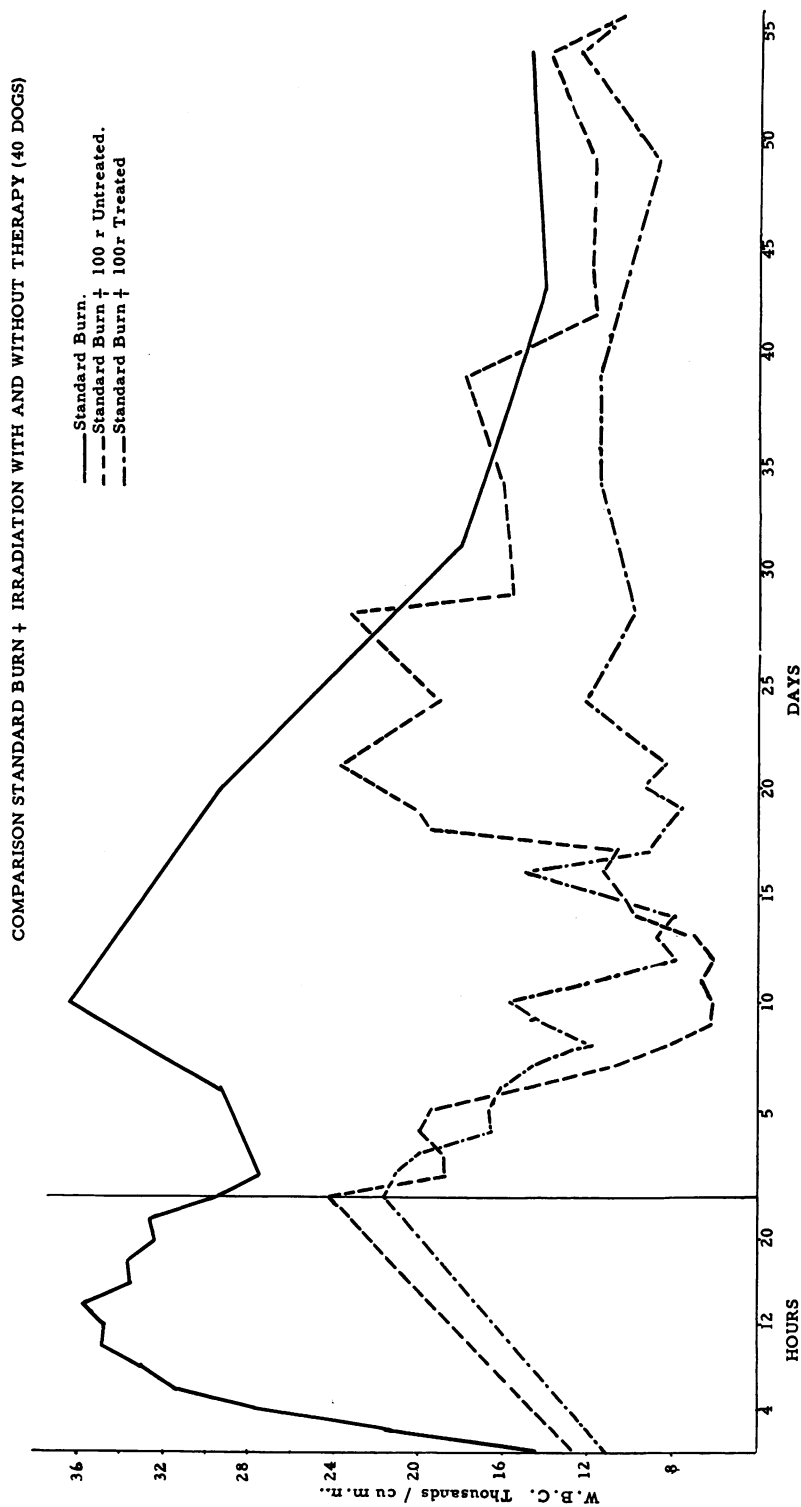


FIG. 4

The mortality rate in this group of 40 dogs was 12 per cent, with death occurring between the fifth and fourteenth days, due usually to infection of pneumonia (Table I).

Many of the specific details of this study may be found in the original article.²

teins, or circulating blood components. The white blood cell count dropped from an average control level of 11,800 W.B.C./cu.mm. to approximately 8300 W.B.C./cu.mm. through the sixth to the twenty-fifth days following radiation. The white

FIG. 5-A

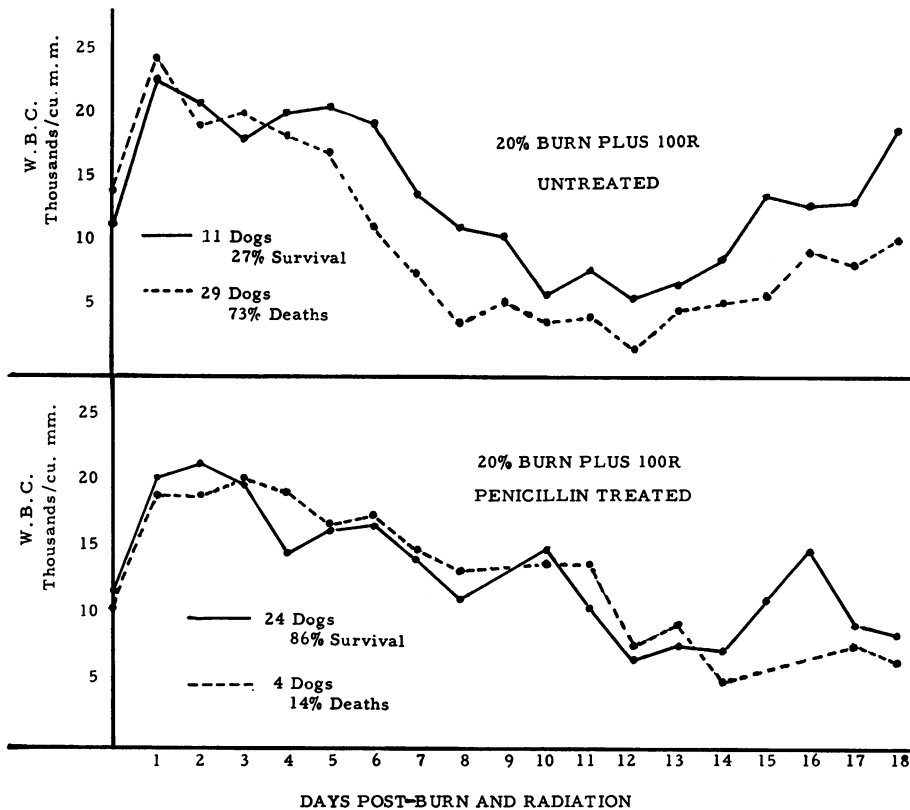


FIG. 5-B

FIG. 5.—Influence of penicillin therapy on thermal, and on combined thermal and radiation injury.

The Effect of 100r External Body Radiation Alone. There was no mortality in the ten animals, five males and five females, which were given total body radiation of 100r without any thermal injury. Clinically no change could be detected in the animals' disposition, activity, appetite, weight, temperature, feces or coat of hair. Microscopic study of the peripheral blood and blood volumes revealed no striking or consistent changes in the red blood cells, plasma pro-

blood cell differential counts showed only a moderate reduction in lymphocytes; no abnormal leukocytes were seen. The bone marrow studies revealed no striking depression or alteration of the marrow activity. No blood cultures were studied in this series.

It can clearly be seen from these observations that total body radiation dosage of 100r is not lethal or even particularly easily detected when it is sustained alone.

Twenty Per Cent Burn Plus 25r External Body Radiation. Similar studies were carried out on combined thermal and ionizing radiation injury, using the standard 20 per cent burn and 25r total body radiation. The mortality in this group was 20 per cent, 25 dogs being included in this group. The healing time of the burns was the same as in previous experiments without external body radiation, that is, six weeks. The white blood cell count never fell below control levels during the period of clinical evi-

found at three weeks following injury. The return of hemoglobin to control level of 15.2 Gm. was gradual, being complete 91 days following injury.

Bone marrow studies showed decreased activity of both myeloid and erythroid elements, up to three weeks following injury.

Although some of the deaths in this series appeared clinically similar to the animals receiving 100r in addition to burn, autopsy findings were negative except for terminal bronchopneumonia.

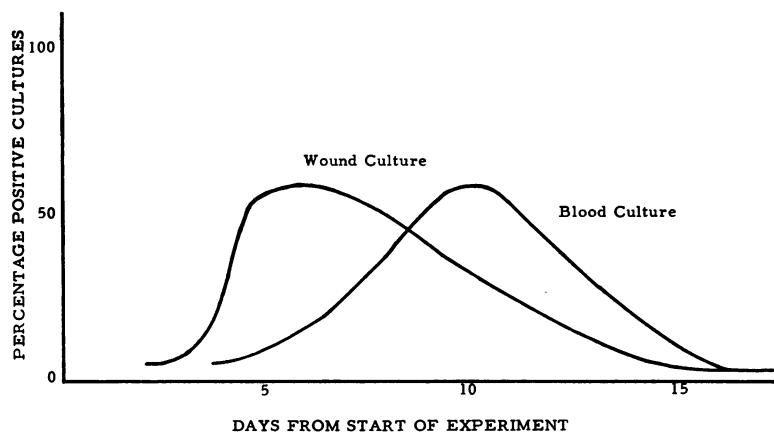


FIG. 6.—Frequency of positive cultures for beta hemolytic *Streptococcus* in untreated dogs.

dence of maximum infection in the burn wound. It was at the lowest levels on the tenth day post burn, reaching then 18,700 W.B.C./cu.mm. this to be compared to an average control level of 14,000 W.B.C./cu.mm. After this the W.B.C. ranged between 21,000 and 27,000 W.B.C./cu.mm. during the first three weeks following burns. Wound and blood cultures were positive for gamma and beta hemolytic streptococci, but death did not occur in all animals developing a beta hemolytic streptococci septicemia.

The anemia reached lower levels sooner than when the burn was inflicted alone but not so soon as in those animals receiving the burn plus 100r. A hemoglobin level of 10.0 Gm. was the low point, this being

Twenty Per Cent Burn Plus 100r External Body Radiation. A total of 40 animals, 25 females and 15 males, were studied. In this group the mortality rate was 73 per cent. No therapy of any type was given to this group. Death occurred between the eighth and fourteenth days post-trauma in most of these animals. In those animals which survived, healing of the burn lesions was complete on an average, by the sixth week post-burning; no detectable difference appeared in rate of wound healing compared to the burn not complicated by radiation.

One of the most striking features of the combined injury was the difference in the total W.B.C. as compared with that found with the burn lesion alone. In the combined injury the W.B.C. on the tenth day follow-

ing injury dropped from an average control value of 12,700 W.B.C./cu.mm. to 6200 W.B.C./cu.mm. The low count is to be compared to the average W.B.C. of 38,000/cu.mm. with the burn lesion alone at the same period following injury (Fig. 4). In those animals that died from the combined injury the W.B.C./cu.mm. on the tenth day was on the average approximately 4000 cells (Table I). Whereas, those animals that lived had an average W.B.C./cu.mm. of 6500 at the same time. Thus, survival or death was apparently little, if at all, influenced by the total peripheral white blood cell count (Fig. 5).

The total peripheral W.B.C. remained below control levels from the seventh day post-trauma through the seventeenth day post-trauma. Following this there was a compensatory leukocytosis which gradually leveled off to approximately normal figures by the sixth week, post-trauma.

In this group of animals, receiving both burn and radiation injury, the blood cultures became positive during the leukopenia phase, first for gamma streptococci and then for beta hemolytic streptococci, in 75 per cent of those animals in which wound and blood cultures were made. All dogs which developed a beta hemolytic streptococci septicemia died; those which did not develop this septicemia did not die (Fig. 6). Serologic typing of the beta hemolytic streptococci indicated that these were animal strains belonging to Groups G and L. The serologic group present in the wound always corresponded with that responsible for the blood stream infection. This information, together with the observation that the same streptococci usually appeared in the wound prior to blood stream invasion, probably incriminates the infected wound as the cause of the bacteremia. Preliminary studies on normal animals have thus far failed to provide sufficient evidence to incriminate any one locality as the normal habitat of either the gamma type or beta

hemolytic streptococci found so uniformly in infected dogs. It has seemed to us that death in those animals is due to the inability of the organism to respond to the great stress of infection because of injury to the bone marrow and possibly to the entire reticulo-endothelial system of bodily defense.

The onset of anemia in these animals receiving the combined injury is more rapid, reaches lower levels, and these lower levels are maintained longer with much slower return to normal than is found with burning alone. Rather profound anemia is present as early as ten days following injury and the hemoglobin remains at low levels until the thirtieth day following injury. This represents a drop from the average control hemoglobin of 15.2 Gm. to a level of 9.9 Gm. which is maintained for three weeks with little change. The slow return to control levels of hemoglobin is gradual and prolonged over double the period required for the 20 per cent burn alone (Figs. 2 and 3).

Bone marrow studies indicate a marked reduction in both myeloid and erythroid series for as long as four weeks post-trauma, with gradual but definite improvement after this time.

Twenty per cent of the animals in this group showed at autopsy evidence of liver injury or dysfunction with jaundice and a small, slate grey liver. Other than Curling's ulcers found in two dogs in this group, little was found at autopsy except terminal bronchopneumonia. Bleeding from the gastro-intestinal tract was the exception rather than the rule, although small petechiae along the longitudinal mucosal folds of the colon were occasionally seen.

EFFECT OF PENICILLIN THERAPY ON COMBINED THERMAL AND IONIZING RADIATION INJURY

A second group of 28 dogs, 18 males and ten females, received a 20 per cent burn and 100r external body radiation. Beginning 24 hours later each dog in this series

was given 900,000 units of Crystacillin once daily intramuscularly for 17 days. This was done to determine how important the beta hemolytic streptococci septicemia was as a cause of death in animals receiving the combined injury. Therapy was delayed 24 hours because we believe that in case of atomic attack, such a delay in antibiotic therapy would necessarily result from the confusion, and an inadequate immediate supply of antibiotic and personnel to administer it. A parenteral rather than an oral antibiotic was chosen for this first therapeutic trial. Later, oral antibiotics will be tried.

The mortality was reduced from the 75 per cent for the combined injury group without therapy to 14 per cent for a similar group with therapy. Wounds healed in four to six weeks, an improvement of one to two weeks in healing time. At ten days following injury, the average total W.B.C./cu.mm. was 15,400, this level being higher than the control level of 11,000 W.B.C./cu.mm. (Table I). However, W.B.C. levels below the control value (as low as 7,700 W.B.C./cu.mm.) were found in this series from the twelfth through the twenty-first days post-trauma (Fig. 4). Thus, penicillin therapy appeared to delay the onset of the severe leukopenia and not allow it to go to levels found in the untreated animals receiving the combined injury.

The hemoglobin level in these treated animals reached its low about the tenth to the twelfth days post-trauma, a drop from 15.0 Gm. to 11.2 Gm. This is earlier than in the other experiments but not as low a level was found. The return to control levels was gradual and complete only by the 120th day post-trauma, approximately the same as the untreated animal with the combined injury (Figs. 2 and 3).

Blood culture studies in this group of penicillin treated animals were all negative.

SUMMARY

Experimental studies have been performed on laboratory animals, dogs, in

which the response to a standard deep second degree burn involving 20 per cent of the skin surface area has been measured. They are reported briefly with reference to the complete study which carries full details. The addition of 100r external body radiation to the standard burn injury has resulted in a sharp increase in mortality in the combined injury. When combined, the mortality increases from 12.0 per cent for the burn alone to 75 per cent with the addition of 100r total body gamma radiation, and to 20 per cent with the addition of 25r total body gamma ray radiation.

Bacteriologic studies indicate that a bacteremia occurs both in dogs experimentally burned as well as in those both burned and radiated. This appears to be a transient phenomenon in the group receiving burns alone, involving streptococci of low virulence and producing a fatal septicemia in only one animal. In the latter group with combined thermal and radiation injury, entrance into the blood of non-hemolytic streptococci is shortly followed by invasion with more virulent beta hemolytic streptococci (dog types G and L) which brings about a fatal septicemia in 75 per cent of the animals. It appears likely that radiation depresses the phagocytic activity and other defense mechanisms to a point where they are unable to localize the beta streptococci at the wound surface.

The beneficial influence of penicillin therapy in reducing sharply the mortality of experimental animals receiving the combined thermal and radiation injury points to the need for provision of this therapy for victims of atomic bomb attacks, and provides the hope that such therapy may reduce the mortality from such combined injury, if external body radiation is limited to those amounts given in this study. The reader is cautioned that the studies and results reported here should not be confused

with those in which lethal amounts of external body radiation (400r or more) are used; with such amounts of radiation body defenses are overwhelmed, and penicillin and other antibiotic therapy is much less effective.

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DISCUSSION.—DR. EVERETT IDRIS EVANS, Richmond: I only want to say that this is one of the earlier parts of a very serious attempt to clarify somewhat the many factors that play on mortality in combined injury from atomic explosions.

It is always well to recall and remember that in general, in wartime and in time of catastrophe, wounds are not very simple, and even without atomic attack, we are left with problems that, when first examined, seem quite simple in nature, but upon really thorough examination get quite complex.

So, with this type of combined study, it should not be peculiar just to those who are interested in atomic injury matters.

Finally, I would just like to pay tribute to Dr. Brooks and the house staff for the really tremendous amount of work they put into these studies, almost at the same time when they were carrying on their routine duties.

It seems, Mr. President, that in our present pessimism regarding the role of the humanities in surgery, it is probably well to recall that probably one of the best merits of man is willingness to work.

DR. FRANK L. MELENEY, New York: I would like to congratulate Dr. Evans and Dr. Brooks for

this fine piece of work. The results are convincing and appear very significant.

I am particularly interested, however, in the simplicity of two things—the simplicity of the bacteriology and the simplicity of the treatment. I would like to ask whether these burned areas were protected with any kind of dressing that would keep them from becoming contaminated with a mixture of organisms.

It seems to me that with atomic injuries there will be a very much more complicated bacteriologic picture which penicillin alone will not be able to control as well as it has in these test cases. In civilian burns as we have seen them—and I am sure it will be even more so, if irradiation injures the local resistance of the tissues against infection—there has always been a great mixture of organisms.

I am surprised, first of all, that staphylococci did not appear more often in the wound cultures, as they usually do, as well as in the blood cultures; and many of them are now resistant to penicillin. Second, it is rather unusual to have the gamma Streptococcus appear in blood cultures, because ordinarily it is not an invasive organism. Third, it is surprising that gram-negative organisms, which so often inactivate penicillin, didn't play an important role.